Claim 26 has been withdrawn from consideration as drawn to non-elected subject matter. Applicants respectfully disagree and thus traverse the requirement and withdrawal.

The elected invention relates to transplantation of insulin producing cells to a patient suffering from insulin dependent diabetes mellitus. This is precisely what claim 26 recites, namely transplanting insulin producing cells in the form of individually coated islets into a patient suffering from IDDM; claim 26 is only slightly more detailed than claim 4 in that claim 26 recites that the transplantation is carried out by injecting the individually isolated islets into the blood stream. It is unreasonable to restrict claim 26 from claims 4, 8, 9 and 11, and applicants respectfully request that claim 26 be examined along with claims 4, 8, 9 and 11.

For the record, applicants note that the corresponding European patent has been granted, such European application having been published December 13, 2006, copy attached.

The previous rejections have been repeated, i.e. claims 4 and 11 have been again rejected as anticipated by both Wagner and Soon-Shiong, individually.[1] The rejections of claims 4 and 11 as anticipated by Wagner and Soon-Shiong are respectfully traversed.

[1] Applicants again respectfully note that claims 8 and 9 have not been so rejected, and applicants accordingly understand that the PTO deems claims 8 and 9 to define novel subject matter over both Wagner and Soon-Shiong.

First, applicants respectfully repeat by reference their Remarks from the preceding Reply in which they have argued against these rejections and pointed out why neither Wagner nor Soon-Shiong anticipate claims 4 and 11, these comments in turn incorporating the Remarks of the Reply of June 30, 2005, the Remarks of March 2, 2004, and the first declaration under 37 CFR 1.132 filed on March 2, 2004. Applicants now respectfully add to those remarks as follows, and support such remarks with applicants' second declaration under 37 CFR 1.132 executed April 2, 2007, and filed herewith.

Thus, as supported by the attached second declaration of the inventors, Wagner and Soon-Shiong do not disclose a method as called for in claim 4 "wherein said individual isolated islets are modified by a reversible adsorption with a clotting inhibiting agent comprising heparin or a fraction or derivative thereof". There is nothing in either Wagner or Soon-Shiong which has anything to do with irreversible adsorption. Respectfully, where is this concept found in either citation? This feature is neither disclosed in the references nor is it inherent[2] in the references, as is further made clear in the attached second declaration of the inventors.

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[2] Insofar as inherency is concerned, any reliance by the PTO on inherency in a reference requires that such inherency must be reasonably certain. For example, please see *In re Brink*, 164 USPQ 247, 249:

> Absent a showing [by the PTO] of some **reasonable certainty** of inherency, the rejection... under 35 U.S.C. 102 must fail. (emphasis added)

Also see *Ex parte Cyba*, 155 USPQ 756, 757 (1967), and *In re Oelrich*, 212 USPQ 323, 326 (1981). Inherency can only be based on reasonable certainty or inevitability.

According to the rejection, Wagner discloses mixing of cells with anticoagulent material before the cells are encapsulated. However, applicants have found no support in Wagner for that statement, and applicants therefore respectfully ask the examiner to point out where this is disclosed.

Applicants have earlier both argued and declared that encapsulation and coating as per the present invention are quite different, and applicants maintain that it is key in understanding the differences between the present invention and the prior art of Wagner and Soon-Shiong to understand the difference in meaning between "encapsulation" and "coating", and to make a correct distinction between encapsulation as per the prior art and coating with heparin as in the present invention. This is the focus of the attached second declaration of the inventors, filed herewith.

Thus, is a distinct physical difference between encapsulated islets and heparin coated islets. The membrane (p. 5, l. 5-9) that "encapsulates" the islets as disclosed by Wagner is an insoluble polymer (see disclosure of polymer films of various types in translated document, p.24 last paragraph and p.25 first paragraph, wherein polyamide, polyester, polyolefins, polysilicones, and polystyrene are disclosed) with a cross-longitudinal network of bonds (which is needed in order to form a membrane). Contrary to this, the Corline Heparin Conjugate which is preferably used in the present invention is a soluble molecule

and each molecule is adsorbed onto the cell surface with no cross-longitudinal linkages between them, thus no membrane is formed. On the contrary, one end of the molecule is adsorbed to the cell and the other end protrudes out from the cell. This is because the molecules are soluble: They preferentially interact with the solvent molecules (water in biological systems), not with other molecules of the same type. Due to this physical characteristic of the present invention, the insulin response by the cell is not delayed, because no membrane barrier has to be penetrated by glucose and insulin.

Further, encapsulation (also referred to as microencapsulation) implies that the islets are confined within a polymer membrane that is not in direct contact with the islets. Even with advanced technology, such as that being used by e.g. Novocell Inc., the capsules leave a dead space of 25-50 μm between the cell surface and the polymer membrane (see fig. 1 in the attached second declaration of the inventors). This creates even more delayed response times due to the fact that glucose must first diffuse through the membrane and then needs to be transported by a concentration gradient across the dead space until it reaches the cell surface.

The insulin response by the cell is delayed and the occurrence of insulin in the blood is further delayed by the dead space and diffusion through the membrane. The end result is that the actual insulin response in blood is too late, and may even

induce hypoglycemia if increased levels of insulin are generated when the glucose levels are already going down.

On the contrary, the Corline Heparin Conjugate preferably used in the present invention is adsorbed directly in close contact with individual islets with no dead space, whereby the glucose in the blood in contact therewith interacts directly with the islet cells so that a physiological response with regard to release of insulin is quickly achieved. Fig. 2 of the inventors' second declaration shows one islet cell coated with heparin according to the present invention and examined by confocal microscopy using fluorescently labelled antithrombin that binds to heparin. It is absolutely clear that the coating follows the contour of the cell and is in direct contact with the cell surface, quite unlike the capsule of the prior art as exemplified by Fig. 1 of such declaration.

Again, it should be and would be very clear to those skilled in the present art that the diffusion characteristics are fundamentally different between the resultant products of the two methods, and that no chemical or technical rationale can be trusted to argue that the use of the Corline Heparin Conjugate would lead to encapsulation.

Claim 11 (dependent on Claim 14) of the present application is related to "Isolated islets comprising insulin producing cells, wherein the islets are individually coated with a clotting inhibiting agent on the islet surface" (Claim 14 of

the present application). According to the above points, the coating according to the present invention is distinctly different from encapsulation (Wagner et al). While the coating according to the present invention is on the islet surface, encapsulation (as disclosed by Wagner and Soon-Shiong) provides a cross-linked barrier inevitably and inherently spaced from and surrounding the islets.

The rejections based on Wagner and Soon-Shiong are unjustified. Applicants respectfully request that these rejections be withdrawn.

Applicants wish to respectfully address one additional point raised in the final action which has applicants puzzled. The final action states as follows at the middle of page 5:

> WO/93/05793 described in the instant specification as modifying the heparin surface is a polymer, and specifically recites the polylysine as a carrier polymer for the heparin. Applicant asserts that the Corline Systems is in reference to a device, the tubing. However, the examiner is not in agreement. The Corline System is drawn to "modified heparin".

Applicants have never denied using Corline Heparin Conjugate, and indeed this is a preferred material, used in example 3. But this has nothing to do with polymer tubing, which tubing was only used as a tool for testing modified islets, such tubing having no function whatsoever in encapsulating any islets, as explained at

page 10 of the last Reply. Thus, applicants' specification states as follows beginning with the last paragraph on page 4:

> All the in vitro experiments for studies of islets contacting whole blood **were performed in a tubing loop model.** [emphasis added]

This clearly concerns only the apparatus or device in which the experiments were conducted.

> A soluble conjugate prepared by covalent binding... of heparin... is irreversibly bonded on to the amine surface of the tubings. ... . By using such heparin modified tubings it is possible to incubate the tubings with non-anticoagulated fresh human blood... . Unmodified tubings will invariably induce complete clotting at these experimental conditions.

The tubings are so prepared in order that they can be used without causing the blood to clot. This provides an appropriate device for carrying out the experiments disclosed in applicants' specification.

Claims 4, 8, 9 and 11 have been rejected under §102(a) as anticipated by Bennet. This rejection is respectfully traversed, in part because Bennet is not "prior art" to the present application.

Bennet is listed as having been published in the **October** 1999 issue of *Diabetes*, and is at least in part based on the work of applicants. It was received for publication on June 1, 1999, and not published until later, i.e. in the October issue.

The present application is entitled to the priority date of applicants' Swedish priority application 9900898-0 filed **February 5, 1999**, well before the earliest possible date of Bennet. Attached hereto is an English language version of applicants' priority application which well supports applicants' claims.

Accordingly, Bennet is not "prior art". Withdrawal of the rejection is in order and is respectfully requested.

All issues raised it the final action are addressed above. Favorable reconsideration, entry of the papers attached, and formal allowance are all respectfully requested.

Respectfully submitted,

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(54) **ISOLIERTE INSLEN, DIE INSULIN-PRODUZIERENDE ZELLEN ENTHALTEN, BESCHICHTETE MIT HEPARIN**

ISOLATED ISLETS, COMPRISING INSULIN PRODUCING CELLS, COATED WITH HEPARIN

ILOTS ISOLES, COMPRENANT DES CELLULES PRODUISANT DE L' INSULINE, ENROBES AVEC L' HEPRARINE

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Description

Field of the invention

[0001] The present invention is within the field of transplantation surgery. More closely, the present invention relates to isolated islets comprising insulin producing cells, characterized by being coated with heparin or heparin conjugate on the islet surface.

Background of the invention

[0002] The only option to achieve permanent normoglycemia in diabetic patients is a renewal of the β-cells, either by transplantation of segmental/whole pancreas or isolated islets of Langerhans. Transplantation of isolated islets is considerably less successful compared to whole pancreas transplantation. The immunological barrier, the underlying autoimmune disease and the immunosuppressive drugs used, are the same in both types of transplantation. Thus, there is no obvious immunological explanation as to why transplantation of whole pancreas is more successful than islet transplantation.

[0003] If, however, the problems related to the unsuccessful outcome of transplantation of islets were identified and a technical and practical solution was developed, obvious benefits for the patients would be created implying interesting commercial opportunities.

[0004] The prior art in this field is largely confined to measures aiming at reducing immunological reactions. WO 9711607 describes transplantation of microencapsulated insulin producing cells as a means of protecting the cells from immunological reactions and/or combined with treating the recipient with a substance that would inhibit an immune-system costimulation. WO 9105855 describes transplantation of islets of animal origin and that the animal tissue should be modified to contain homologous complement restriction factors. DE 19623 440 Al describes methods for encapsulation of islets and points out that the artificial encapsulation material may induce platelet activation, coagulation and complement activation, and therefore the encapsulation material should be modified to allow release of inhibiting substances as e.g., heparin, hirudin or Marcumar. US 5 635 178 is not related to transplantation of islets but describes monoclonal antibodies having inhibitory activity towards the terminal complex of complement and that such antibodies can be used to reduce activation of platelets and endothelial cells.

[0005] It is evident for those skilled in the art that measures aiming at inhibiting immunological reactions in connection with transplantation of islets regardless of being allogenic or xenogenic have not lead to a satisfactory result in respect of clinical outcome.

Summary of the invention

[0006] The present inventors have performed experiments implying adding human, adult porcine or fetal porcine islets to human whole blood and have been struck by the vigorous coagulation occurring when these islets were injected into human ABO-compatible blood. As judged by microscopical examinations it is evident that the islets are rapidly coated by a layer of platelets which soon develops into an organised thrombus. This biological event has previously not been considered and is now suggested to be a major explanation as to why the outcome of autologous islet transplantation has been comparatively unsuccessful. The present invention is related to measures to reduce this incompatibility reaction that can either be directed towards inhibiting activation of platelets, mono- or polymorhonuclear cells or the enzyme cascade of coagulation. Regardless of the initiating event, any of these reactions will lead to generation of thrombin, which eventually converts fibrinogen to fibrin. The generation of thrombin can easily be monitored by measuring the thrombin- antithrombin complex (TAT complex).

[0007] Hence, the present invention is concerned with therapeutic measures to inhibit TAT complex formation upon exposure of allogenic or xenogenic islets to whole blood.

[0008] Therefore, the present invention relates to isolated islets comprising insulin producing cells, characterized by being coated with heparin or a heparin conjugate on the islet surface. The isolated islets comprise islets of Langerhans.

[0009] In one embodiment of the invention, the islet cells are coated by preincubation of islets in a solution containing heparin. Using a conjugate of heparin to coat the islets, it was demonstrated that the modified islets had acquired an increased capacity to adsorb antithrombin and loop experiments (described below) demonstrated that it is possible to reduce clotting by using such modified islets.

[0010] A combination of heparin or a heparin conjugate and inhibitor of platelet activation can be used according to the invention or any other suitable combination of heparin or a heparin conjugate. Optionally heparin or a heparin conjugate is supplemented by an inhibitor of complement.

[0011] Furthermore, the invention relates to a method of modification of isolated islets for treatment of insulin dependent diabetes mellitus, IDDM, comprising coating isolated cells with heparin or a heparin conjugate.

Detailed description of the invention

[0012] The invention will be described more closely below in association with the accompanying drawings, in which

Fig. 1 is a graph showing percent aggregation of platelets following addition of islets to platelet rich plasma, PRP, as a function of time;

Fig. 2 shows a similar graph as in Fig. 1 but here a RGDS (standard one letter code for amino acids) tetrapeptide was added to PRP before islets were added; and

Fig. 3 shows a similar graph as in Figs. 1 and 2 but here a monoclonal antibody against the Fc receptor on platelets was added to PRP before islets were added.

[0013] All the in vitro experiments for studies of islets contacting whole blood were performed in a tubing loop model. The experimental model is a modification of a model for testing biomaterials that has previously been described (J. Clin. Immunol. 16, 223-230 (1996)). Tubings made of polyvinylchloride (PVC, i.d. = 6.3 mm, length = 300 mm) were modified with immobilized heparin according to a method developed by Corline Systems AB (Uppsala, Sweden) as disclosed in international patent application no WO93/05793. Briefly, the polymer surface is modified with a high molecular weight amine compound to add primary amine groups to the surface. A soluble conjugate prepared by covalent binding of approximately 60 mol of heparin per mol of a straight-chained polyallylamine is irreversibly bonded onto the amine surface of the tubings. This procedure results in a total surface concentration of heparin of approximately 0.5 $\mu g/cm^2$. By using such heparin modified tubings it is possible to incubate the tubings with non-anticoagulated fresh human blood in a rocking device at 37°C for one hour with only moderate activation of blood (c.f. control column in Table 1 A and 1 B below). Unmodified tubings will invariably induce complete clotting at these experimental conditions. Addition of human islets or porcine adult or fetal islets lead to some remarkable observations. Complete clotting invariably occurred with a total loss of platelets, a sharp increase in the formation of TAT and a very significant increase in the markers of the early contact phase (FXIIa and FXIa) of coagulation (C.f. Table 1 A and 1 B). Histological examination revealed a dense layer of activated platelets immediately adjacent to the capsule of the islets.

[0014] The findings in vitro described above were confirmed in vivo by evaluation of porcine islets after intraportal transplantation in pigs. The porcine livers, removed 60 min. after islet transplantation, had a congested appearance with patchy dark discoloration's on the surface. In the portal veins blood clots were found, with a patchy adherence to the endothelium, and branching into the portal tree, partially occluding the vessels. The histological examination revealed islets entrapped in blood clots, with a disrupted islet morphology. Occasionally a fibrin tail could be observed extending away from the islet.

[0015] With reference to Table 1 B, it appears that the effect of adding an inhibitor of complement leads to reduced activation of complement, as expected, but there is no measurable effect on the clotting of blood or activation of platelets. If, however, soluble heparin was added to the experimental system there was a remarkable improvement in preservation of the number of platelets and reduced generation of TAT.

[0016] In another set of experiments the effects of inhibiting the interaction between platelet integrins and their specific ligands were investigated. With reference to Fig. 1-3, it appears that platelet aggregation is induced upon contact with islets and that such aggregation can be prevented by blocking platelet integrins or Fc-receptors.

[0017] Porcine islets were surface modified by incubation in a buffered solution containing a high molecular weight conjugate of heparin (Corline Heparin Conjugate), as disclosed in WO 93/05793, and then rinsed by changing buffer several times. It was demonstrated that the modified islets had acquired an increased capacity to adsorb antithrombin and loop experiments showed that heparin modified islets resulted in reduced clotting compared to unmodified islets.

[0018] The following non-limiting Examples are only used to demonstrate the principle behind the present invention.

Example 1: Effect of soluble heparin (Not part of the invention)

[0019] Sixty ml of non-anticoagulated blood was collected from healthy blood donors using heparin-coated equipment. U-shaped tubings with a total volume of nine ml were filled with eight ml of blood immediately followed by addition of isolated human islets or porcine adult or porcine fetal islets (500 IEQ). The tubings were then closed into loops using connectors of titanium furnished with immobilised heparin. The tubing loops were placed vertically in a rocking device and the complete apparatus was placed in an incubator at 37°C for up to sixty minutes. At the end of the rocking period blood was collected in EDTA and the number of cells were counted in a automatic cell counter. The blood samples were then centrifuged at 4°C (3290xg, 20 min) and EDTA plasma was collected and immediately put at -70°C. Islets retrieved after blood perifusion were prepared for immunohistochemistry. The results are summarized in Table 1A and 1B below.

[0020] Table 1A shows results of blood cell counts and coagulation and complement parameters before and after 60

min. of human islet perifusion with ABO-compatible fresh human blood or blood supplemented with heparin.

Table 1A

Table 1A: Blood cell counts and coagulation and complement parameters before and after 60 min. of human islet perifusion with ABO-compatible fresh human blood or blood supplemented with heparin.

	BEFORE	CONTROL	HUMAN ISLETS	
			WITHOUT ADDITIVES	HEPARIN
Platelets ($x10^9$)	233 ± 13.8	161.1 ± 9.3	5 ± 0.3***	114 ± 17*
Neutro. ($x10^9$)	3.23 ± 0.33	3.03 ± 0.32	0.83 ± 0.18***	2.56 ± 0.43
Mono. ($x10^9$)	0.36 ± 0.03	0.36 ± 0.04	0.03 ± 0.01***	0.28 ± 0.06
Lymph. ($x10^9$)	1.91 ± 0.12	1.77 ± 0.12	1.29 ± 0.12**	1.60 ± 0.20
C3a (ng/mL)	84 ± 4.7	507 ± 115	1259 ± 125.1 ***	565 ± 143.6
C5b-9 (AU/mL)	15.6 ± 2.9	95 ± 30	213 ± 43.4*	147 ± 39.6
FXHA-AT (umol/L)	0.09 ± 0.01	0.36 ± 0.15	12.9 ± 0.9***	5.4 ± 1.7**
FXIa-AT (umol/L)	0.06 ± 0.01	0.12 ± 0.03	4.74 ± 0.48***	0.34 ± 0.12*
TAT (ug/mL)	12.5 ± 5.2	316 ± 100	20537 ± 1973***	4467 ± 2285

Control loops contained blood and culture medium (RPMI), but no islets. All values are stated as the Mean ± SE(M). TAT, Thrombin-antithrombin. The degree of significance is reported with respect to the controls.
(*p<0.05; **p<0.01; ***p<0.001; n.a. = not analysed).

[0021] Table I B shows results of blood cell counts and coagulation and complement parameters before and after 60 min. of adult and fetal porcine islet perifusion with fresh human blood or blood supplemented with the complement inhibitor C1 inactivator (C1-INA) or heparin.

Table 1B: Blood cell counts and coagulation and complement parameters before and after 60 min. of adult and fetal porcine islet perifusion with fresh human blood or blood supplemented with C1-INA or heparin.

	BEFORE	CONTROL	ADULT ISLETS			FETAL ISLETS
			WITHOUT ADDITIVE	C1-INA	HEPARIN	WITHOUT ADDITIVES
Platelets ($x10^9$)	237 ± 8.0	171 ± 9.0	4 ± 0.1***	4 ± 0	145 ± 13.	4 ± 0***
Neutrophils ($x10^9$)	2.75 ± 0.21	2.52 ± 0.21	0.57 ± 0.07***	0.41 ± 0.13	3.00 ± 0.19	1.44 ± 0.17*
Monocytes ($x10^9$)	0.38 ± 0.02	0.37 ± 0.02	0.04 ± 0.01***	0.15 ± 0.01	0.35 ± 0.05	0.07 ± 0.01***
Lymphcytes ($x10^9$)	2.30 ± 0.14	2.13 ± 0.11	1.74 ± 0.10*	1.23 ± 0.38	1.88 ± 0.11	1.68 ± 0.25
C3a (ng/mL)	80.1 ± 7.3	545 ± 68	1435 ± 173***	1094 ± 78	486 ± 139	1601 ± 215***
C5b-9 (AU/mL)	15.8 ± 1.8	72 ± 10	283 ± 34***	183 ± 29	82 ± 22	302 ± 46***
FXIIa-AT (mmol/L)	0.18 ± 0.03	0.13 ± 0.00	8.96 ± 1.38***	19.65 ± 0.45	3.56 ± 1.60**	n.a.
FXIa-AT (mmol/L)	0.04 ± 0.00	0.03 ± 0.00	4.14 ± 0.48***	2.95 ± 0.15	0.53 ± 0.26	n.a.

(continued)

	BEFORE	CONTROL	ADULT ISLETS			FETAL ISLETS
			WITHOUT ADDITIVE	C1-INA	HEPARIN	WITHOUT ADDITIVES
TAT (ug/mL)	5.6 ± 1.1	139 ± 35	23886 ± 3494***	30250 ± 3450	505 ± 162***	34420 ± 4875

Control loops contained blood and culture medium (RPMI), but no islets. All values are stated as the Mean SE(M). TAT, Thrombin-antithrombin. The degree of significance is reported with respect to the controls. (*p<0.05; **p<0.01; ***p<0.001; n.a..= not analysed).

[0022] C 1 inactivator reduced complement activation but had no detectable effect on the coagulation parameters. Soluble heparin, however, prevented clotting and there was a remarkable improvement with respect to platelet count and generation of TAT. Notwithstanding the results obtained by the use of CI-INA, it is obvious that it should be beneficial to combine an anticoagulant with an inhibitor of complement.

Example 2: Effect of platelet inhibitor (Not part of the invention)

[0023] Platelets in platelet rich plasma (PRP) and gel filtered platelets were tested in an aggregometer. Islets were added to PRP and thereafter analysed in the aggregometer. It was shown that the islets induced aggregation of the platelets (Fig. 1) and that platelets number in the sample were reduced from 375 x 10^9 to 236 x 10^9. If purified platelets without plasma proteins were used in combination with islets no aggregation and reduction in the platelet count were observed. In attempts to identify the mechanism behind the induced aggregation, an RGDS tetrapeptide to inhibit integrin binding and a monoclonal antibody against Fc recpetors on platelets were used. Addition of the RGDS peptide totally abolished the aggregation and the consumption of platelets when islets were added to PRP (Fig. 2). A similar finding was obtained if the anti-Fc receptor antibody was added (Fig. 3).
Conclusion: The experiments show that islets bind to platelets when added to PRP. This binding induce activation and aggregation of the platelets.

Example 3: Effect of surface modification of islets using a heparin conjugate

[0024] Using Corline Heparin Conjugate (c.f. WO 93/05793) containing approximately sixty mol of heparin covalently bound to one mol of straight-chained carrier, adult porcine islets were modified by irreversible adsorption of the heparin conjugate onto the surface of the islets. This was accomplished by incubating the islets for 30 minutes at 37°C in a buffered saline solution containing heparin conjugate.

[0025] The presence of heparin at the surfaces of the islets was demonstrated by an ELISA assay for islet surface associated antithrombin (AT). Unmodified and heparin modified islets were incubated in human plasma for thirty minutes and then rinsed several times by changing buffer. The islet were then incubated with anti-AT that had been labelled with biotin. Using HRP-labelled streptavidin the uptake of anti-AT could be semiquantitatively estimated. The uptake of anti-AT on the heparin modified islets was three times higher than that on the unmodified islets showing that biologically active heparin was present on the surface of the islets. Testing of heparin modified islets in the tubing loop model resulted in less clotting compared to unmodified islets.

[0026] The present invention is expected to significantly improve the situation for IDDM patients. By surface modification of islets, optionally together with administration of a complement inhibitor, in association with transplantation of insulin producing cells it is expected that the need of providing these patients with injections of insulin will be substantially decreased or even eliminated.

Claims

1. Isolated islets comprising insulin producing cells, **characterized by** being coated with heparin or a heparin conjugate on the islet surface.

2. Isolated islets according to claim 1, wherein the heparin or the heparin conjugate is/are supplemented by an inhibitor of complement.

3. Isolated cells comprising islets of Langerhans, **characterized by** being coated with a heparin conjugate on the islet surface.

4. Method of modification of isolated islets for treatment of insulin dependent diabetes mellitus, IDDM, comprising coating isolated islets with heparin or heparin conjugate.

5. Method according to claim 4, wherein islet cells are coated by preincubation of islets in a solution containing heparin or heparin conjugate.

Patentansprüche

1. Isolierte Inseln umfassend Insulin produzierende Zellen, **dadurch gekennzeichnet, dass** sie auf der Oberfläche der Inseln mit Heparin oder einem Heparinkonjugat beschichtet sind.

2. Die isolierten Inseln gemäß Anspruch 1, worin das Heparin oder Heparinkonjugat mit einem Komplementinhibitor ergänzt ist.

3. Isolierte Inseln umfassend Langerhanssche Inseln, **dadurch gekennzeichnet, dass** sie auf der Oberfläche der Inseln mit einem Heparinkonjugat beschichtet sind.

4. Verfahren zur Modifizierung von isolierten Inseln zur Behandlung von Insulinabhängigem Diabetes mellitus, IDDM, umfassend Beschichten isolierter Inseln mit Heparin oder Heparinkonjugat.

5. Das Verfahren gemäß Anspruch 4, wobei Inselzellen mittels Vorinkubation von Inseln in einer Lösung beschichtet werden, die Heparin oder Heparinkonjugat enthält.

Revendications

1. Ilots isolés comprenant des cellules de production d'insuline, **caractérisés en ce qu'**ils sont revêtus d'héparine ou d'un conjugué d'héparine sur la surface de l'îlot.

2. Ilots isolés selon la revendication 1, dans lesquels l'héparine ou le conjugué d'héparine est/sont ajouté(s) par un inhibiteur de complément.

3. Ilots isolés comprenant des îlots de Langerhans, **caractérisés en ce qu'**ils sont revêtus d'un conjugué d'héparine sur la surface de l'îlot.

4. Procédé de modification d'îlots isolés pour le traitement du diabète insulinodépendant (DID), consistant à revêtir des îlots isolés d'héparine ou d'un conjugué d'héparine.

5. Procédé selon la revendication 4, dans lequel les îlots de Langerhans sont revêtus par préincubation des îlots dans une solution contenant de l'héparine ou un conjugué d'héparine.

Fig. 1

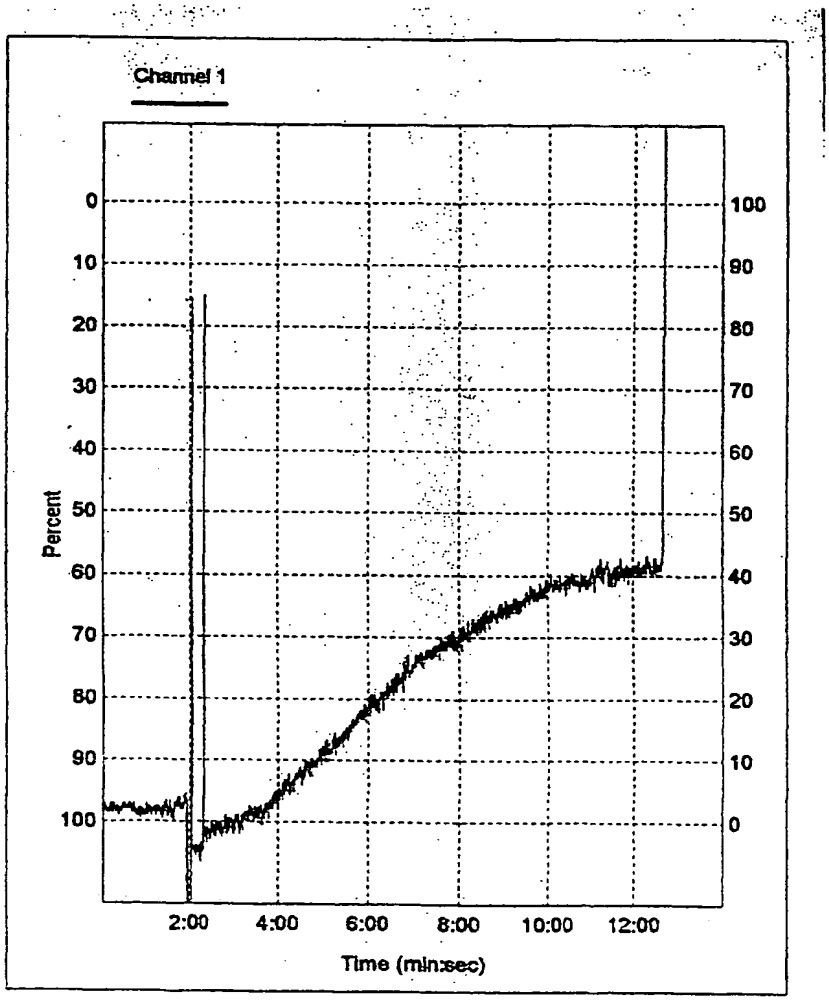
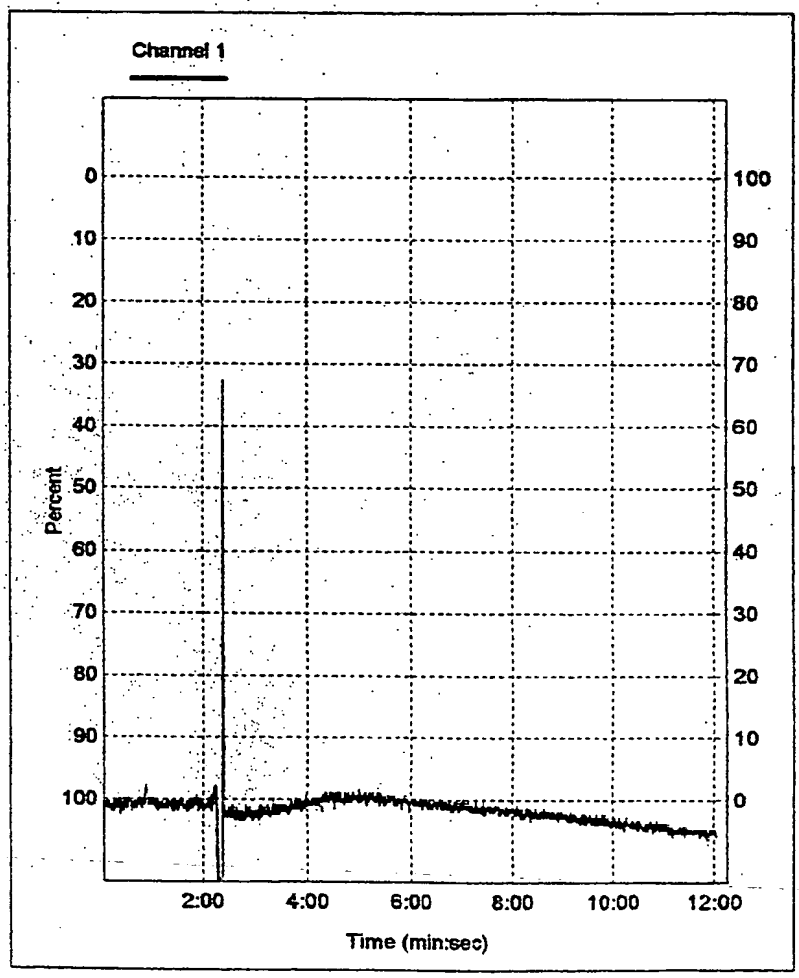


Fig. 2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2:00
4:00
6:00
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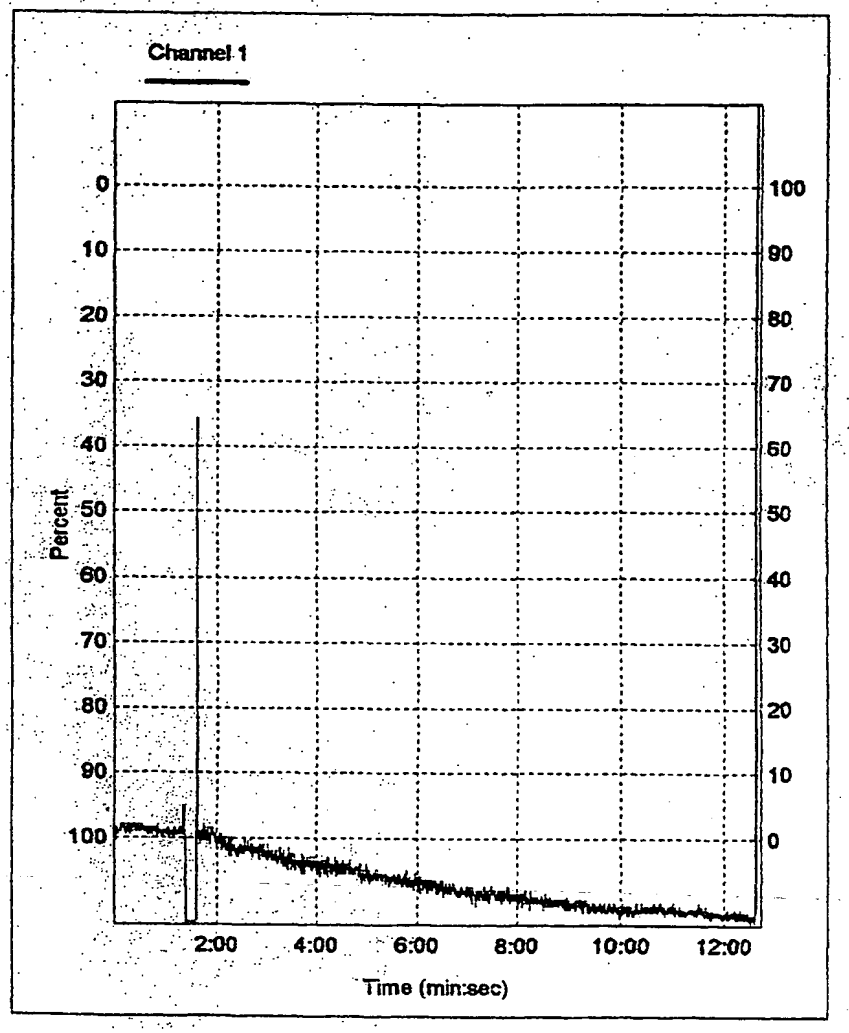
10:00
12:00
Time (min:sec)

Fig. 3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